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ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

View Article Online
DOI: 10.1039/C6RA11171H

A new more atom-efficient multi-component approach to tetrasubstituted imidazoles: One-pot condensation of nitriles, amines and benzoin

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Abstract

A new more atom-efficient multi-component approach for the synthesis of tetrasubstituted imidazoles *via* the one-pot condensation of nitriles, primary amines and benzoin has been described. Using this method, a wide range of structurally diverse nitriles and primary amines were successfully condensed with benzoin in glycerol in the presence of TFA under microwave irradiation at 120 ^{o}C and all products were obtained in good to excellent yields with higher atom efficiencies in comparison with the commonly used four-component condensation of aldehydes, ammonium acetate, primary amines and benzil.

Introduction

Between various kinds of heterocyclic compounds, imidazoles occupied a special place because of their unique biological properties such as anti-inflammatory[1], inhibition of p38 MAP kinase[1], anti-allergic[2] and analgesic activity.[3] Their presence in so many natural products and biological active compounds such as histidine and histamine (two human body essential amino acids) and their versatile applications as sensitizers of multi-drug-resistant cancer cells[4], pesticides[5], antibiotics[6] and sodium channel modulators[7a,b] have been caused to increased importance of these molecules. Moreover, imadazoles are the main backbone of some commercial drugs such as ketoconazole[7c] as an antifungal and losartan[7d] as an anti-hypertension agent. In addition to their biological and pharmaceutical applications, these compounds have been attracted much attention in benign organic synthesis due to

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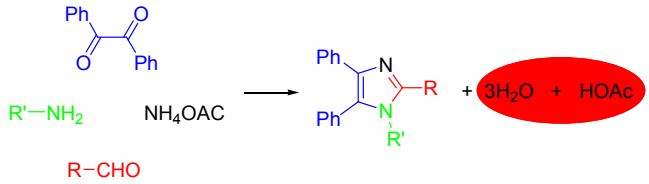
DOI: 10.1039/C6RA11171H

their application as more green solvents by means of imidazolium-based ionic liquids[8] and in organometallic chemistry as *N*-heterocyclic carbenes.[9] From the first report about the preparation of imidazoles in 1858[10] to now, various synthetic strategies have been applied for the synthesis of these compounds.[11] Although there are a wide variety of synthetic routes toward imidazoles, only a few studies exist for the synthesis of 1,2,4,5-tetrasubstituted imidazoles which are mostly performed *via* multi step routes[1d, 1f-g, 12] or *via* a trisubstituted 1*H*-imidazole in which the nitrogen is substituted in the final step.[3, 13] Nowadays, the most commonly used synthetic route to tetrasubstituted imidazoles is a one-pot four-component reaction of benzil, aldehydes, primary amines and ammonium acetate (Scheme 1) under various reaction condition.[14]



Scheme 1. The one-pot four-component route to tetrasubstituted imidazoles.

In spite of the fact that the application of this method is in combination with advantages of multi-component synthesis, unfortunately, it has the fatal problem of low atom efficiency due to the waste of three molecules of water and one molecule of acetic acid (Scheme 1). So, despite the available one-pot four-component method, there still exists a demand for the devising a more atom-efficient and environmentally benign route which allows the simple and fast synthesis of tetrasubstituted imidazoles.

Based on the above facts and as a part of our recent studies in the development of more benign procedures for the synthesis of heterocyclic compounds[15], we herein report a new and more atom-efficient three-component reaction for the synthesis of tetrasubstituted imidazols *via* a one-pot condensation of nitriles (**1**), primary amines (**2**) and benzoin (**3**) in the presence of catalytic amounts of trifluoroacetic acid (TFA) under microwave irradiation. (Scheme 2)

Experimental

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All chemicals were purchased from Merck, Fluka and Aldrich chemical companies and used without further purification. ^{1}H (250 and 300 MHz) and ^{13}C-NMR (62.5 and 75 MHz) spectra were recorded on Bruker Avance 250 and Bruker Avance 300 spectrometers in DMSO-d_6 solution with tetramethylsilane (TMS) as an internal standard. Microanalysis was performed on a Perkin-Elmer 240-Bmicroanalyzer. Mass spectra were recorded on a Shimadzu GC MS-QP 1000 EX apparatus. Melting points were determined in open capillary tubes with a Barnstead Electro-thermal 9100 BZ circulating oil melting point apparatus. The reaction monitoring was accomplished by TLC on silica gel PolyGram SILG/UV254 plates. All reactions were carried out using a laboratory microwave oven (MicroSYNTH, Milestone Company, Italy). The reactions were performed in a glass tube sealed with a septum. The reported reaction temperature was monitored using a calibrated infrared temperature control mounted under the reaction vessel. The reaction mixture was magnetically stirred. All reactions were performed three times and the average amount of isolated yields and reaction times were reported.

General procedure for the condensation of benzoin, nitriles and primary amines

A solution of nitrile (**1**) (1 mmol), primary amine (**2**) (1 mmol), benzoin (**3**) (1 mmol) and TFA (0.1 mmol, 0.01 g) in glycerol (5 mL) was placed in a pressure-resistance microwave glass tube sealed with a septum. The mixture was stirred for 5 min at room temperature and exposed to microwave irradiation (300 W) at 120 ^{o}C (The microwave instrument was set to increase the temperature to 120 ^{o}C during 1 min.) and the progress of reaction was monitored by TLC (In order to check the progress of the reaction, the microwave irradiation was stopped each one minute, the reaction mixture was cooled to room temperature and the TLC analysis was taken place. If the reaction was not completed, the reaction vessel has been sealed and the reaction temperature was increased to 120 ^{o}C during 1 minutes and after this, the microwave irradiation was taken place for another one minute. These steps were repeated until the reaction became completed. Then, the reaction time was calculated as the sum of each one minute of microwave irradiations. After this, a new mixture of the same starting materials was continuously irradiated with microwave irradiation for calculated time and the completion of the reaction was checked at the end. In all cases, obtained results were the same.). After the completion of reaction, the mixture was cooled to room temperature, water (20 mL) was added and resulting solids were filtered

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off and washed with hot water (10 mL) and dried under reduced pressure. Purer products were obtained with recrystallization from hot ethanol.

Selected Spectral Data

1-(4-isopropylphenyl)-2,4,5-triphenyl-1*H*-imidazole (4b)

White powder, ^{1}H NMR (250 MHz, DMSO-d_6) δ (ppm) 1.09 (d, J= 6.8 Hz, 6H), 2.82 (m, 1H), 7.13-7.46 (m, 19H). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ (ppm) 22.9, 32.4, 123.5, 124.3, 126.9, 127.2, 127.4, 128.0, 128.5, 128.6, 129.0, 129.4, 129.5, 130.0, 130.2, 130.8, 132.9, 133.2, 135.9, 144.7, 146.2. Anal. Calcd. for $C_{30}H_{26}N_2$: C, 86.92; H, 6.32; N, 6.76 (%). Found: C, 86.97; H, 6.24; N, 6.83 (%). MS (*m/z*): 414 (M^+).

1-benzyl-2,4,5-triphenyl-1*H*-imidazole (4d)

White powder, ^{1}H NMR (250 MHz, DMSO-d_6) δ (ppm) 5.12 (s, 2H), 6.70-7.63 (m, 20H). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ (ppm) 50.4, 126.9, 127.3, 127.4, 127.9, 128.5, 128.6, 128.8, 128.9, 129.2, 129.4, 129.7, 129.9, 130.3, 131.4, 132.4, 132.9, 136.7, 142.3, 150.9. Anal. Calcd. for $C_{28}H_{22}N_2$: C, 87.01; H, 5.74; N, 7.25 (%). Found: C, 86.91; H, 5.83; N, 7.30 (%). MS (*m/z*): 386 (M^+).

1-(4-methoxyphenyl)-2,4,5-triphenyl-1*H*-imidazole (4e)

White powder, ^{1}H NMR (250 MHz, DMSO-d_6) δ (ppm) 3.67 (s, 3H), 6.80-7.36 (m, 19H). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ (ppm) 53.4, 114.3, 123.4, 127.3, 128.1, 128.4, 128.6, 128.8, 129.1, 129.4, 129.7, 130.1, 130.4, 130.7, 131.0, 133.0, 133.52, 133.59, 146.2, 158.4. Anal. Calcd. for $C_{28}H_{22}N_2O$: C, 83.56; H, 5.51; N, 6.96 (%). Found: C, 83.45; H, 5.49; N, 7.08 (%). MS (*m/z*): 402 (M^+).

4-(1-benzyl-4,5-diphenyl-1*H*-imidazol-2-yl)phenol (4p)

White powder, ^{1}H NMR (250 MHz, DMSO-d_6) δ (ppm) 5.08 (s, 2H), 6.71-7.46 (m, 19H), 9.83 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ (ppm) 49.9, 116.5, 123.9, 126.9, 127.4, 127.7, 128.3, 128.74, 128.79, 128.9, 129.01, 129.03, 129.5, 129.8, 132.3, 134.5, 137.0, 141.8, 150.9, 158.7. Anal. Calcd. for $C_{28}H_{22}N_2O$: C, 83.56; H, 5.51; N, 6.96 (%). Found: C, 83.61; H, 5.60; N, 7.09 (%). MS (*m/z*): 402 (M^+).

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4-(1,4,5-triphenyl-1*H*-imidazol-2-yl)phenol (4q)

White powder, ^{1}H NMR (250 MHz, DMSO-d_6) δ (ppm) 6.60-6.65 (m, 2H), 7.13-7.47 (m, 17H), 9.77 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ (ppm) 116.2, 123.9, 125.8, 127.2, 127.9, 128.0, 128.8, 128.9, 129.0, 129.3, 129.5, 129.8, 130.5, 133.0, 133.4, 136.1, 141.9, 158.9. Anal. Calcd. for $C_{27}H_{20}N_2O$: C, 83.48; H, 5.19; N, 7.21 (%). Found: C, 83.36; H, 5.05; N, 7.39 (%). MS (*m/z*): 388 (M^+).

4-(1-(4-methoxyphenyl)-4,5-diphenyl-1*H*-imidazol-2-yl)phenol (4r)

White powder, ^{1}H NMR (250 MHz, DMSO-d_6) δ (ppm) 3.79 (s, 3H), 6.79 (d, J= 8.7 Hz, 2H), 6.94 (d, J= 8.7 Hz, 2H), 7.22-7.61 (m, 14H), 9.67 (br, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ (ppm) 54.9, 114.9, 115.9, 124.4, 126.0, 126.9, 128.3, 128.8, 129.0, 129.3, 129.4, 129.7, 131.0, 132.9, 133.03, 133.09, 149.0, 158.5, 159.4. Anal. Calcd. for $C_{28}H_{22}N_2O_2$: C, 80.36; H, 5.30; N, 6.69 (%). Found: C, 80.47; H, 5.24; N, 6.73 (%). MS (*m/z*): 418 (M^+).

4-(1-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazol-2-yl)phenol (4s)

White powder, ^{1}H NMR (250 MHz, DMSO-d_6) δ (ppm) 6.67-6.70 (m, 2H), 7.19-7.46 (m, 16H), 9.67 (br, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ (ppm) 116.3, 123.9, 125.6, 126.9, 128.8, 128.9, 129.1, 129.3, 129.4, 129.5, 129.8, 130.0, 130.6, 133.0, 133.1, 134.0, 136.4, 147.2, 158.7. Anal. Calcd. for $C_{27}H_{19}ClN_2O$: C, 76.68; H, 4.53; N, 6.62 (%). Found: C, 76.55; H, 4.62; N, 6.74 (%). MS (*m/z*): 422 (M^+).

1-benzyl-2-(4-methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (4t)

White powder, ^{1}H NMR (250 MHz, DMSO-d_6) δ (ppm) 2.28 (s, 3H), 5.11 (s, 2H), 6.69-7.52 (m, 19H). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ (ppm) 47.8, 53.1, 112.3, 123.4, 127.0, 127.3, 127.5, 128.60, 128.61, 128.7, 129.0, 129.2, 129.4, 129.7, 131.0, 132.5, 132.9, 137.3, 140.9, 152.2, 160.5. Anal. Calcd. for $C_{29}H_{24}N_2O$: C, 83.63; H, 5.81; N, 6.73 (%). Found: C, 83.72; H, 5.70; N, 6.76 (%). MS (*m/z*): 416 (M^+).

2-(4-tert-butylphenyl)-1-benzyl-4,5-diphenyl-1*H*-imidazole (4u)

White powder, ^{1}H NMR (250 MHz, DMSO-d_6) δ (ppm) 1.25 (s, 9H), 5.11 (s, 2H), 6.72-7.55 (m, 19H). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ (ppm) 29.9, 33.8, 28.1, 124.0, 125.9, 126.3, 126.4, 127.3, 127.4,

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127.5, 127.6, 128.3, 128.5, 128.6, 128.7, 131.4, 131.8, 135.3, 140.5, 150.1, 150.3. Anal. Calcd. for $C_{32}H_{30}N_2$: C, 86.84; H, 6.83; N, 6.33 (%). Found: C, 86.76; H, 6.94; N, 6.27 (%). MS (*m/z*): 442 (M^+).

2-(4-bromophenyl)-4,5-diphenyl-1-*p*-tolyl-1*H*-imidazole (4v)

White powder, ^{1}H NMR (250 MHz, DMSO-d_6) δ (ppm) 2.25 (s, 3H), 7.09-7.51 (m, 18H). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ (ppm) 21.0, 119.9, 124.8, 127.5, 128.3, 128.4, 129.0, 129.3, 129.5, 130.1, 131.1, 132.3, 132.5, 133.3, 136.3, 141.3, 148.6. Anal. Calcd. for $C_{28}H_{21}BrN_2$: C, 72.26; H, 4.55; N, 6.02 (%). Found: C, 72.33; H, 4.69; N, 5.93 (%). MS (*m/z*): 464 (M^+).

1-(4-isopropylphenyl)-2-(4-nitrophenyl)-4,5-diphenyl-1*H*-imidazole (4w)

White powder, ^{1}H NMR (250 MHz, DMSO-d_6) δ (ppm) 1.11 (d, *J*= 6.7 Hz, 6H), 2.82 (m, 1H), 7.10-7.44 (m, 14H), 7.86 (d, *J*= 7.0 Hz, 2H), 8.29 (d, *J*= 7.0 Hz, 2H). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ (ppm) 22.9, 32.4, 124.6, 124.8, 126.0, 126.9, 127.2, 128.3, 128.5, 128.8, 129.3, 129.6, 129.7, 130.0, 130.5, 131.9, 132.5, 137.1, 143.5, 148.4, 148.6. Anal. Calcd. for $C_{30}H_{25}N_3O_2$: C, 78.41; H, 5.48; N, 9.14 (%). Found: C, 78.33; H, 5.59; N, 9.25 (%). MS (*m/z*): 459 (M^+).

2-(4-(1-benzyl-4,5-diphenyl-1*H*-imidazol-2-yl)phenyl)-1*H*-benzo[*d*]imidazole (4x)

White powder, ^{1}H NMR (250 MHz, DMSO-d_6) δ (ppm) 6.52 (s, 2H), 6.80-7.65 (m, 23H), 12.92 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ (ppm) 46.9, 113.2, 115.3, 120.6, 120.7, 124.7, 125.22, 125.29, 125.3, 125.9, 126.1, 126.2, 126.3, 126.5, 126.6, 127.12, 127.16, 127.3, 127.5, 130.2, 130.7, 134.2, 138.9, 139.4, 149.2, 153.4. Anal. Calcd. for $C_{35}H_{26}N_4$: C, 83.64; H, 5.21; N, 11.15 (%). Found: C, 83.57; H, 5.30; N, 11.01 (%). MS (*m/z*): 502 (M^+).

4,5-bis(4-chlorophenyl)-2-(4-methoxyphenyl)-1-phenyl-1*H*-imidazole (4ab)

White powder, ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 3.79 (s, 3H), 7.08 (d, J= 7.5 Hz, 2H), 7.43-7.51 (m, 6H), 7.58-7.63 (m, 3H), 7.73-7.78 (m, 4H), 7.91 (d, *J*= 7.5 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 54.8, 113.8, 124.3, 124.9, 127.5, 128.0, 128.9, 129.6, 130.8, 131.0, 131.25, 131.29, 132.9, 134.8, 135.3, 135.9, 136.1, 138.9, 150.0, 160.7. Anal. Calcd. for $C_{28}H_{20}Cl_2N_2O$: C, 71.34; H, 4.28; N, 5.94; (%). Found: C, 71.28; H, 4.31; N, 5.99 (%). MS (*m/z*): 471 (M^+).

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1,2-diphenyl-4,5-di-*p*-tolyl-1*H*-imidazole (4af)

White powder, ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 2.17 (s, 6H), 7.09 (d, J= 7.5 H, 4H), 7.39-7.58 (m, 12H), 7.81 (d, J= 7.5 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 20.5, 123.7, 127.5, 127.8, 127.91, 127.99, 129.0, 129.3, 129.4, 129.6, 129.9, 130.0, 130.2, 131.0, 134.0, 136.1, 136.5, 138.9, 139.4, 150.1. Anal. Calcd. for $C_{29}H_{24}N_2$: C, 86.97; H, 6.04; N, 6.99; (%). Found: C, 86.89; H, 6.12; N, 6.83 (%). MS (*m/z*): 400 (M^+).

4-(1-benzyl-4,5-diphenyl-1*H*-imidazol-2-yl)benzonitrile (6a)

White powder, m.p= 197-199 ^{o}C. ^{1}H NMR (250 MHz, DMSO-d_6) δ (ppm) 5.18 (s, 2H), 7.01-7.29 (m, 15H), 7.66 (d, J= 7.8 Hz, 2H), 7.93 (d, J= 7.8 Hz, 2H). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ (ppm) 49.1, 111.5, 117.6, 126.8, 127.1, 127.8, 128.3, 128.7, 128.9, 129.0, 129.7, 129.8, 129.9, 130.2, 131.3, 132.9, 133.5, 135.9, 140.9, 152.0. Anal. Calcd. for $C_{29}H_{21}N_3$: C, 84.64; H, 5.14; N, 10.21 (%). Found: C, 84.57; H, 5.23; N, 10.10 (%). MS (*m/z*): 411 (M^+).

1-benzyl-2-(4-(1-benzyl-4,5-diphenyl-1*H*-imidazol-2-yl)phenyl)-4,5-diphenyl-1*H*-imidazole (6b)

White powder, m.p.= 289-292 (dec.). ^{1}H NMR (250 MHz, DMSO-d_6) δ (ppm) 5.66 (s, 2H), 7.00-7.75 (m, 34H). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ (ppm) 49.9, 127.7, 128.2, 128.3, 129.1, 129.2, 129.3, 129.5, 130.1, 130.3, 130.4, 130.5, 133.2, 133.7, 137.2, 142.4, 152.2. Anal. Calcd. for $C_{50}H_{38}N_4$: C, 86.42; H, 5.51; N, 8.06 (%). Found: C, 86.50; H, 5.38; N, 8.10 (%).

1,2-diphenyl-2-(phenylamino)ethanone (8a)

Yellowish powder, m.p.= 167-168 ^{o}C. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 4.94 (s, 1H), 5.49 (s, 1H), 6.34 (d, J= 6.5 Hz, 2H), 6.43 (t, J= 7.5 Hz, 1H), 6.75 (t, J= 7.5 Hz, 2H), 7.11-7.40 (m, 8H), 7.55 (d, J= 7.5 Hz, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm) 64.1, 112.1, 117.2, 126.2, 126.9, 127.1, 127.4, 127.7, 131.7, 134.8, 135.1, 144.3, 192.2. Anal. Calcd. for $C_{20}H_{17}NO$: C, 83.59; H, 5.96; N, 4.87 (%). Found: C, 83.67; H, 5.83; N, 4.90 (%).

(*Z*)-*N*′-phenylbenzamidine (9a)

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Yellowish powder, m.p.= 112-113 °C (110-111 °C)[18]. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 4.87 (s, 2H), 6.95 (d, *J*= 6.6 Hz, 2H), 7.06 (t, *J*= 6.6 Hz, 1H), 7.30 (t, *J*= 6.6 Hz, 2H), 7.39 (t, *J*= 6.2 Hz, 2H), 7.50 (t, *J*= 6.2 Hz, 1H), 7.85 (d, *J*= 6.2 Hz, 2H). ^{13}C NMR (62.5 MHz, CDCl3) δ (ppm) 121.8, 123.6, 126.1, 128.7, 130.2, 136.2, 150.5, 154.8. Anal. Calcd. for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.27 (%). Found: C, 79.49; H, 6.21; N, 14.40 (%).

Results and Discussion

In the first step, we focused on the search of a catalytic system for the condensation reaction between nitriles, primary amines and benzoin. For this purpose, the condensation reaction between benzonitrile (1 mmol), aniline (1 mmol) and benzoin (1 mmol) for the synthesis of compound (**4a**) was selected as a model reaction and the yield of product and the time of reaction were monitored in the presence of different catalytic systems under various reaction conditions and obtained results were summarized in Table 1.

Table 1. The condensation reaction of benzonitrile (1 mmol), aniline (1 mmol) and benzoin (1 mmol) in the presence of various catalysts under different reaction conditions.

Entry	Catalyst (quantity)	Reaction Conditions	Time	Yield (%)[a]
1	-	Solvent-free, 140 °C	24 (h)	No reaction
2	[Bmim]Br (0.5 g)	140 °C	24 (h)	Trace
3	[Bmim]HSO_4 (10 mol%)	Solvent-free, 140 °C	18 (h)	35[b]
4[c]	PEG-OSO_3H (10 mol%)	Solvent-free, 140 °C	24 (h)	30
5[d]	Silica sulfuric acid (0.5 g)	Solvent-free, 140 °C	24 (h)	38
6	SiO_2/P_2O_5 - 5% w/w (0.5 g)	Solvent-free, 140 °C	24 (h)	30
7	$NaHSO_4.SiO_2$ (10 mol%)	Solvent-free, 140 °C	24 (h)	Trace
8	$Zn(OAc)_2$ (10 mol%)	Solvent-free, 140 °C	24 (h)	Trace
9	$Ni(OAc)_2$ (10 mol%)	Solvent-free, 140 °C	24 (h)	Trace

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10	HOAc (5 mL)	Reflux	12 (h)	61
11	TFA (10 mol%)	Solvent-free, 140 ^{o}C	8 (h)	71
12	TFA (2 mol%)	Solvent-free, 140 ^{o}C	24 (h)	51
13	TFA (5 mol%)	Solvent-free, 140 ^{o}C	16 (h)	58
14	TFA (15 mol%)	Solvent-free, 140 ^{o}C	8 (h)	71
15	TFA (10 mol%)	Ethanol (5 mL), Reflux	24 (h)	40
16	TFA (10 mol%)	Methanol (5 mL), Reflux	24 (h)	38
17	TFA (10 mol%)	DMF (5 mL), Reflux	15 (h)	62
18	TFA (10 mol%)	THF (5 mL), Reflux	24 (h)	25
19	TFA (10 mol%)	Solvent-free, 120 ^{o}C	14 (h)	70
20	TFA (10 mol%)	Solvent-free, 150 ^{o}C	8 (h)	71
21	TFA (10 mol%)	Glycerol (5mL), 80 ^{o}C, MW (300 w)	20 (min)	75
22	TFA (10 mol%)	Glycerol (5 mL), 100 ^{o}C, MW (300 w)	14 (min)	88
23	TFA (10 mol%)	Glycerol (5 mL), 120 ^{o}C, MW (300 w)	10 (min)	89
24	TFA (10 mol%)	Glycerol (5 mL), 120 ^{o}C, MW (100 w)	20 (min)	72
25	TFA (10 mol%)	Glycerol (5 mL), 120 ^{o}C, MW (200 w)	20 (min)	82
26	TFA (10 mol%)	Glycerol (5 mL), 120 ^{o}C, MW (400 w)	10 (min)	89
27	TFA (10 mol%)	Glycerol (5 mL), 140 ^{o}C, MW (300 w)	10 (min)	88
28	TFA (10 mol%)	Solvent-free, 120 ^{o}C, MW (300 w)	20 (min)	83

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[a] Isolated yield. [b] The reaction was not proceeded more even after 24 h. [c] For more information about this catalyst please see Ref. 16a, b. [d] For more information about this catalyst please see Ref. 16c.

After extensive screening, the best yield and time profile were obtained with 10 mol% of TFA under solvent-free condition at 140 ^{o}C, which furnished the corresponding tetrasubstituted imidazol (**4a**) in 71% yield within 8h (Table 1, entry 11). Increasing the amount of TFA to more than 15 mol % showed no substantial improvement in the yield (Table 1, entry 14), whereas the yield decreased and reaction time increased by the decreasing the amount of the catalyst (Table 1, entries 12 and 13). The reaction did not proceed efficiently in the absence of TFA after a long time (24 h) (Table 1, entry 1).

There are many investigations on the critical role of microwave irradiation on the rate acceleration and yield enhancement of various chemical reactions.[17] Considering this fact, we decided to examine our methodology under microwave irradiation to improve the overall yield of the reaction. For this purpose, the model reaction was subjected to microwave irradiation in the presence of TFA (10 mol%) at various temperatures. Moreover, in order to enhance the microwave irradiation efficiency, glycerol has been applied as a benign and nonvolatile microwave active reaction medium and obtained results are summarized in Table 1. The optimum reaction conditions were found to be 120 °C for 10 min with the maximum power of 300 W and desired product (**4a**) was obtained in 89% yield (Table 1, entry 23). Increasing the temperature and microwave irradiation power did not affect the yield of product or reaction time (Table 1, entries 26 and 27).

With the optimized conditions in hand, the scope and efficiency of the process were explored with the one-pot condensation of a broad range of structurally diverse aromatic nitriles as well as primary amines (aliphatic or aromatic) with benzoin under microwave irradiation (Scheme 2), and the results are displayed in Table 2.

Table 2. The one-pot condensation of nitriles (1 mmol), primary amines (1 mmol) and benzoin (1 mmol) in the presence of TFA (10 mol%) in glycerol (5 mL) under microwave irradiation (300 w) at 120 ^{o}C.

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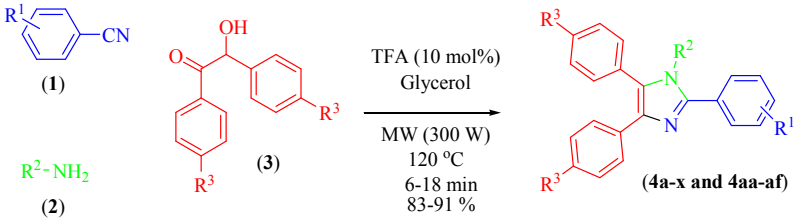

Scheme 2. The new more atom-efficient one-pot three-component route to tetrasubstituted imidazoles.

Entry	R^1	R^2	R^3	Time (min)	Yield (%)[a]	M.P. (°C)	
						Found	Reported[Ref.]
4a	H	C_6H_5	H	10	89	218-220	219-221[14w]
4b	H	*p*-$CH(CH_3)_2$-C_6H_4	H	10	91	152-155	-
4c	H	CH_3	H	10	91	146-147	144-146[14w]
4d	H	$C_6H_5CH_2$	H	10	90	155-158	157-159[14w]
4e	H	*p*-OCH_3-C_6H_4	H	7	90	239-241	-
4f	*p*-CH_3	CH_3	H	10	90	214-215	210-213[14w]
4g	*p*-CH_3	*Iso*-C_4H_9	H	13	84	150-152	155-156[14w]
4h	*p*-CH_3	C_6H_5	H	13	88	189-190	191-193[14w]
4i	*p*-CH_3	$C_6H_5CH_2$	H	10	91	163-164	166-168[14w]
4j	*p*-Br	CH_3	H	15	90	202-204	200-203[14w]
4k	*m*-NO_2	*p*-CH_3-C_6H_4	H	7	83	145-147	145-147[14w]
4l	*p*- NO_2	*p*-CH_3-C_6H_4	H	7	85	219-221	215-217[14w]
4m	*p*-Cl	$C_6H_5CH_2$	H	10	90	160-162	161-163[14w]
4n	*p*-CH_3	*p*-CH_3-C_6H_4	H	10	90	190-192	194-196[14w]
4o	*p*-Cl	$C_6H_5CH_2$	H	6	91	145-147	149-151[14w]
4p	*p*-OH	$C_6H_5CH_2$	H	15	89	135-138	136-138[14w]
4q	*p*-OH	C_6H_5	H	18	86	280-282	283-284[14w]
4r	*p*-OH	*p*-OCH_3-C_6H_4	H	15	90	> 300	-
4s	*p*-OH	*p*-Cl-C_6H_4	H	18	90	290-292	-
4t	*p*-OCH_3	$C_6H_5CH_2$	H	15	91	167-169	-
4u	*p*-$C(CH_3)_3$	$C_6H_5CH_2$	H	13	86	177-179	-
4v	*p*-CH_3	*p*-Br- C_6H_4	H	12	91	217-219	-
4w	*p*-NO_2	*p*-$CH(CH_3)_2$-C_6H_4	H	7	86	195-198	-

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4x	*p*-(bezimiazole-2-yl)	$C_6H_5CH_2$	H	15	88	254-256	-
4y	H	*p*-NO_2-C_6H_4	H	30	-	-	-
4z	H	*o*-NO_2-C_6H_4	H	30	-	-	-
4aa	*p*-CH_3	$C_6H_5CH_2$	*p*-Cl	15	89	186-188	185-186[14p]
4ab	*p*-OCH_3	C_6H_5	*p*-Cl	17	85	169-171	-
4ac	H	C_6H_5	*p*-OCH_3	30	-	-	-
4ad	*p*-NO_2	$C_6H_5CH_2$	*p*-OCH_3	30	-	-	-
4ae	*p*-OCH_3	$C_6H_5CH_2$	*p*-CH_3	12	89	180-182	183-184[14p]
4af	H	C_6H_5	*p*-CH_3	18	86	173-174	-

[a] Isolated yield.

As it is shown in Table 2, all reactions were proceeded in very short times (6-18 min) and in all cases desired products were obtained in good to excellent yields (83-91%). Based on the obtained results it can be concluded that the existence of electron withdrawing groups on the aromatic ring of nitriles was lead to the enhancement of the reaction rate (Table 2, entries 4k, 4l and 4w) whereas the existence of electron donating groups was lead to the decreasing of the reaction rates (Table 2, entries 4p, 4q, 4r, 4s, 4t). Moreover, it has been observed that the reaction was not proceeded with the application of aromatic primary amines with a strong electron withdrawing groups (NO_2 substituent at the para and or ortho position of aromatic ring) even after a long time of microwave irradiation (30 min) (Table 2, entries 4y and 4z). Besides, this method can be successfully applied for the halide or alkyl substituted benzoins (Table 2, entries 4aa, 4ab, 4ae and 4af). Unfortunately, only a mixture of unknown products was obtained with the application of methoxy (as an electron donating group) substituted benzoin even after a long time of microwave irradiation (30 min) (Table2, entries 4ac and 4ad). All obtained products were fully characterized by ^{1}H NMR and ^{13}C NMR spectroscopy and by comparison with the reported spectral data.

Interestingly, this method can be easily applied for the condensation of primary amines (**2**) and benzoin (**3**) with bis(cyanide)s such as terephthalonitrile (**5**) (Scheme 3). The reaction of 1 equivalent of banzoin (**3**) and benzylamine (**2a**) with terephthalonitrile (**5**) proceeded rapidly to give mono-imidazole (**6a**) and bis-imidazole (**6b**) in 91% and trace yields after 10 minutes, respectively. On the other hand,

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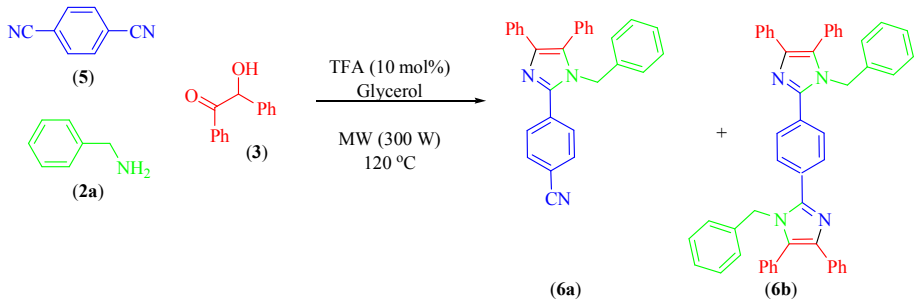
using 2 equivalents of benzoin (**3**) and benzylamine (**2a**) afforded compounds (**6a**) and (**6b**) in trace and 88% yields after 14 minutes, respectively, under similar reaction conditions (Scheme 3).



Scheme 3. The one-pot condensation of benzoin (**3**) and benzylamine (**2a**) with terephthalonitrile (**5**) in the presence of TFA (10 mol%) in glycerol under microwave irradiation (300 W) at 120 °C.

The selectivity of presented method in the synthesis of tetrasubstituted imidazoles can be explained by two different mechanistic pathways that are shown in Scheme 4.

In the first step of pathway A, an imine intermediate (**7**) produces from the condensation of primary amine (**2**) and benzoin (**3**) and readily tautomerized to an α-amino carbonyl compound (**8**). In the next step, desired tetrasubstituted imidazole (**4**) will be formed with the nucleophilic attack of α-amino carbonyl compound (**7**) to the nitrile (**1**) that will be followed with an intramolecular nucleophilic cyclization. In the first step of pathway B, an arylamidine (**9**) produces from the nucleophilic attack of amine (**2**) to the nitrile (**1**) and in the next step desired tetrasubstituted imidazole (**4**) will be produced with the condensation of aryamidine (**9**) with benzoin (**3**) (Scheme 4).

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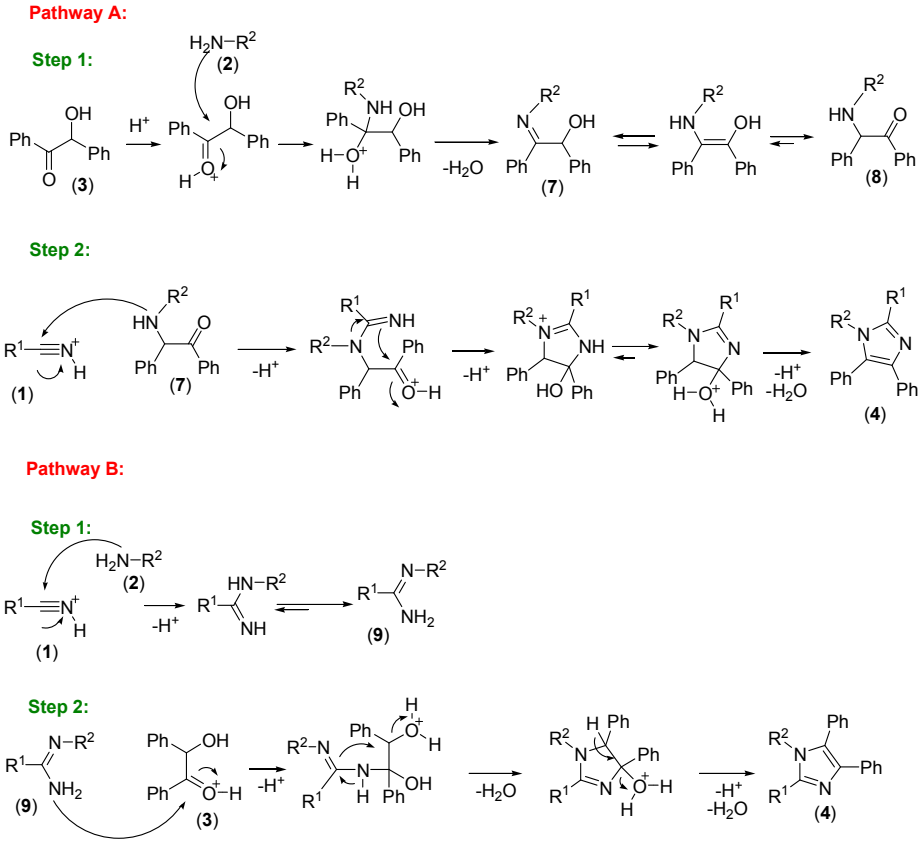

Scheme 4. The plausible mechanisms for one-pot three-component condensation of nitriles, primary amines and benzoin in the presence of TFA under microwave irradiation.

The authenticity of suggested pathways was studied with the conduction of two examinations (Scheme 5). In the first examination, a mixture of benzoin (**3**) (1 mmol) and aniline (**2b**) (1mmol) in glycerol (5 mL) was irradiated (300 W) in the presence of TFA (10 mol%) at 120 ^{o}C. The progress of the reaction was monitored by TLC. After the completion of the reaction, products were separated and purified with plate chromatography and identified with ^{1}H and ^{13}C NMR. The obtained results from ^{1}H and ^{13}C NMR studies established the correct structure of 1,2-diphenyl-2-(phenylamino)ethanone (**8a**) (an α-aminocarbonyl compound) as it has been expected based on the pathway A. In the next step, isolated 1,2-diphenyl-2-(phenylamino)ethanone (**8a**) was reacted with benzocyanide (**1a**) under optimized reaction conditions and related tetrasubstituted imidazole (**4a**) was obtained as the only product of the reaction as it has been expected by pathway A (Scheme 5). In order to examine the

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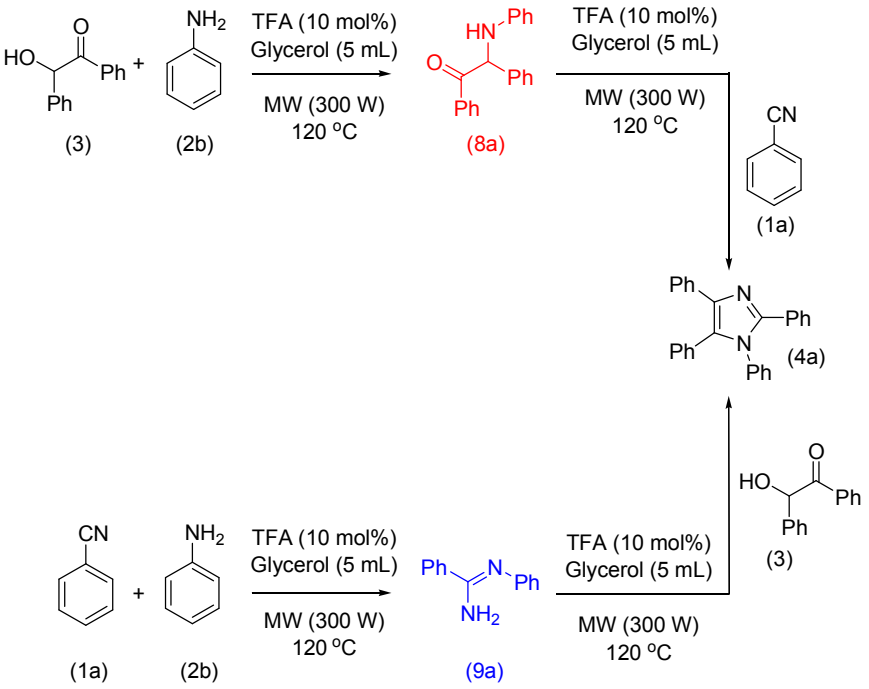
authenticity of pathway B, a mixture of benzocyanide (**1a**) (1 mmol) and aniline (**2b**) (1 mmol) in glycerol (5 mL) was irradiated (300 W) in the presence of TFA (10 mol%) at 120 °C. The progress of the reaction was monitored by TLC. After completion of reaction, products were separated and purified by plate chromatography and identified with ^{1}H and ^{13}C NMR. Obtained results from ^{1}H and ^{13}C NMR studies established the correct structure of (*Z*)-*N*′-phenylbenzamidine (**9a**) as it has been expected based on the pathway B. In the next step, isolated (*Z*)-*N*′-phenylbenzamidine (**9a**) was reacted with benzoin (**3**) under optimized reaction conditions and related tetrasubstituted imidazole (**4a**) was obtained as the only product of the reaction as it has been expected by pathway B (Scheme 5). Based on these observations, both of pathways A and B are possible and will be occurred during the one-pot condensation of nitriles, primary amines and benzoin in the presence of TFA in glycerol under microwave irradiation at 120 °C.



Scheme 5. The study of pathways A and B authenticity.

In another study, the atom efficiency of our presented method was compared with the atom efficiencies of previously reported four-component methods for the synthesis of tetrasubstituted imidazoles and obtained results are summarized in Table 3. As it is obviously shown in Table 3, the

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atom efficiency of presented method is distinctly higher than the other reported four-component methods.

Table 3. The comparative atom efficiency of previously reported four-component methods and presented method for the synthesis of compound (**4a**).

Entry	Conditions	Atom Efficiency	Ref.
1[a]	Trityl chloride (10 mol%), 90 ^{o}C, Solvent-free	60	14u
2[a]	SiO_2, Microwave irradiation, Solvent-free	60	14j
3[a]	Nanocrystalline $MgAl_2O_4$ (0.035 mol%), EtOH, Ultrasonic Irradiation	69	14n
4[a]	$InCl_3.3H_2O$ (10 mol%), MeOH, Room Temperature	62	14a
5[a]	SiO_2-BF_3, 140 ^{o}C, Solvent-free	68	14b
6[a]	[Bmim]Br, Microwave irradiation	68	14w
7[b]	TFA (10 mol%), Microwave irradiation, Solvent-free	81	This work

[a] Benzil (1 mmol), benzaldehyde (1 mmol), aniline (1 mmol) and NH_4OAc (1 mmol). [b] Benzoin (1 mmol), benzonitrile (1 mmol) and aniline (1 mmol).

So briefly, a new more atom-efficient approach for one-pot multi-component synthesis of tetrasubstituted imidazoles is presented. In this method, nitriles were successfully condensed with benzoin and primary amines in a one-pot approach in the presence of trifluoroacetic acid under microwave irradiation in glycerol at 120 ^{o}C. The promising points for the presented methodology are higher atom efficiencies, generality, high yields, short reaction times, clean reaction profile, ease of product isolation, application of microwave as a renewable energy source, and finally agreement with some of green chemistry protocols.

Acknowledgement

We gratefully appreciate the Shiraz University Research Councils for the financial support of this work.

References

1. (a) P. P. Graczyk, A. Khan, G. S. Bhatia, V. Palmer, D. Medland, H. Numata, H. Oinuma, J. Catchick, A. Dunne, M. Ellis, C. Smales, J. Whitfield, S. J. Neame, B. Shah, D. Wilton, L. Morgan, T. Patel, R. Chung, H. Desmond, J. M. Staddon, N. Sato and A. Inoue, *Bioorg. Med. Chem. Lett.* 2005, **15**, 4666;

View Article Online
DOI: 10.1039/C6RA11171H

(b) S. A. Laufer, W. Zimmermann and K. J. Ruff, *J. Med. Chem.* 2004, **47**, 6311; (c) G. M. Sperandio da Silva, C. M. R. Sant QAnna and E. J. Barreiro, *Bioorg. Med. Chem.* 2004, **12**, 3159; (d) J. A. Murry, *Curr. Opin. Drug Discov. Dev.* 2003, **6**, 945; (e) J. C. Lee, J. T. Laydon, P. C. McDonnell, T. F. Gallagher, S. Kumar, D. Green, D. McNulty, M. J. Blumenthal, J. R. Keys, S. W. L. Vatter, J. E. Strickler, M. M. McLaughlin, I. R. Siemens, S. M. Fisher, G. P. Livi, J. R. White, J. L. Adams and P. R. Young, *Nature* 2002, **372**, 739; (f) K. M. Marcantonio, L. F. Frey, D. Frantz, J. Murry, A. Soheili, R. Tillyer, E. J. J. Grabowski, P. Reider, 224th ACS National Meeting, Boston, MA, USA, August18-22, 2002; (g) S. Laufer, G. Wagner and D. Kotschenreuther, *Angew. Chem. Int. Ed.* 2002, **41**, 2290; (h) N. J. Liverton, J. W. Butcher, C. F. Clairborne, D. A. Claremon, B. E. Libby, K. T. Nguyen, S. M. Pitzenberger, H. G. Selnick, G. R. Smith, A. Tebben, J. P. Vacca, S. L. Varga, L. Agarwal, K. Dancheck, A. J. Forsyth, D. S. Fletcher, B. Frantz, W. A. Hanlon, C. F. Harper, S. J. Hofsess, M. Kostura, J. Lin, S. Luell, E. A. Neill, C. J. Orevillo, M. Pang, J. Parsons, A. Rolando, Y. Sahly, D. M. Visco and S. J. Keefe, *J. Med.Chem.* 1999, **42**, 2180.

2. J. W. Black, G. J. Durant, J. C. Emmett and C. R. Ganellin, *Nature* 1974, **248**, 65.

3. R. Uaucu, N. G. Karaburun and I. Isikdag, *Farmaco* 2001, **56**, 285.

4. A. Mjalli, S. Sarshar, U. S. Patent **1997**, US 5700826, pp 19.

5. Y. Niwano, H. Koga, H. Kodama, K. Kanai, T. Miyazaki and H. Yamaguchi, *Med. Mycol.* 1999, **37**, 351.

6. M. Antolini, A. Bozzoli, C. Ghiron, G. Kennedy, T. Rossi and A. Ursini, *Bioorg. Med. Chem. Lett.* 1999, **9**, 1023.

7. (a) A. Liberatore, J. Schulz, J. Pommier, M. Barthelemy, M. Huchet, P. Chabrier and D. Bigg, *Bioorg. Med. Chem. Lett.* 2004, **14**, 3521; (b) D. W. Cheung and E. E. Daniel, *Nature* 1980, **283**, 485; (c) J. Heeres, L. J. J. Backx, J. H. Mostmans and J. Van Cutsem, *J. Med. Chem.* 1979, **22**, 1003; (d) P. R. Conlin, W. C. Gerth, J. Fox, J. B. Roehm and S. J. Boccuzzi, *Clin. Ther.* 2001, **23**, 1999.

8. (a) P. Wasserscheid and T. Welton, (Eds.) Ionic Liquids in Synthesis,Wiley VCH, Weinheim, 2003; (b) T. Welton, *Chem. Rev.* 1999, **99**, 2071.

9. (a) H. L. Lee, M. Bang and C. S. Pak, *Tetrahedron Lett.* 2005, **46**, 7139; (b) J. M. D. Storey and C. Williamson, *Tetrahedron Lett.* 2005, **46**, 7337; (c) W. A. Herrmann, *Angew. Chem. Int. Ed.* 2002, **41**,

View Article Online
DOI: 10.1039/C6RA11171H

1290; (d) D. Bourissou, O. Guerret, F. P. Gabba and W. G. Bertrand, *Chem. Rev.* 2000, **100**, 39; (e) W. A. Herrmann and C. Kçcher, *Angew.Chem. Int. Ed. Eng.* 1997, **36**, 2162.

10. R. M. Acheson, (Ed.) An Introduction to the Chemistry of Heterocyclic Compounds, John Wiley and Sons, New York. 1967.

11. G.W. Gribble, J. A. Joule and T. L. Gilchrist, (Eds.) Progress in Heterocyclic Chemistry, volume 13-17, Elsevier, Oxford. 2001-2005.

12. (a) W. Li and Y. J. Lam, *Comb. Chem.* 2005, **7**, 644; (b) Y. M. Losksha, A. A. El-Barbary, M. A. El-Badawi, C. Nielsen and E. B. Pedersen, *Bioorg. Med. Chem.* 2005, **13**, 4209; (c) J. A. Murry, D. Frantz, L. Frey, A. Soheili, K. Marcantonio, R. Tillyer, E. J. J. Grabowski and P. J. Reider, *ACS Sym. Ser.* 2004, **870**, 161; (d) O. A. Attanasi, L. DeCrescentini, G. Favi, P. Filippone, F. Mantellini and S. Santeusanio, *Synlett* **2**004, 549; (e) H. Zhong, S. Dubberke, S. Muller, A. Rossler, T. W. Schulz, D. J. Korey, T. Otten, D. G. Walker and A. Abdel-Magid, *PCT Int. Appl*. 2002, WO02/076974, pp 55 ; (f) H. B. Lee and S. Balasubramanian, *Org.Lett.* 2000, **2**, 323.

13. P. Deprez, E. Mandine, A. Vermond and D. Lesuisse, *Bioorg.Med. Chem. Lett.* 2002, **12**, 1287.

14. (a) S. D. Sharma, P. Hazarika and D. Konwar, *Tetrahedron Lett.* 2008, **49**, 2216; (b) B. Sadeghi, B. F. Mirjalili and M. M. Hashemi, *Tetrahedron Lett.* 2008, **49**, 2575; (c) M. M. Heravi, F. Derikvand and F. F. Bamoharram, *J. Mol. Catal. A: Chem.* 2007, **263**, 112; (d) S. Kantevari, S. V. N. Vuppalapati, D. O. Biradar and L. Nagarapu, *J. Mol. Catal. A: Chem.* 2007, **266**, 109; (e) M. Kidwai, P. Mothsra, V. Bansal and R. K. Somvanshi, *J. Mol. Catal. A: Chem.* 2007, **265**, 177; (f) L. Nagarapu, S. Apuri and S. Kantevari, *J. Mol. Catal. A: Chem.* 2007, **266**, 104; (g) A. R. Karimi, Z. Alimohammadi and J. Azizian, *Catal. Commun.* 2006, **7**, 728; (h) M. M. Heravi, F. Derikvand and M. Haghighi, *Monatsh. Chem.* 2008, **139**, 31; (i) D. R. J. Acke, R. V. A. Orru and C. V. Stevens, *QSAR Comb. Sci.* 2006, **25**, 474; (j) S. Balalaie, A. Arabanian, *Green Chem.* 2000, **2**, 274; (k) G. V. M. Sharma, Y. Jyothi and P. S. Lakshmi, *Synth. Commun.* 2006, **36**, 2991; (l) A. R. Karimi, Z. Alimohammadi and M. M. Amini, *Mol. Divers.* 2010, **14**, 635; (m) K. Niknam, A. Deris, F. Naeimi and F. Majleci, *Tetrahedron Lett.* 2011, **52**, 4642; (n) J. Safari, S. Gandomi-Ravandi and Z. Akbari, *J. Adv. Res.* 2013, **4**, 509; (o) A. Javid, M. M. Heravi, F. F. Bamoharram and M. Nikpour, *E-Journal Chem.* 2011, **8**, 547; (p) S. Samai, G. C. Nandi, P. Singh and M. S. Singh, *Tetrahedron*. 2009, **65**, 10155; (q) R. A. Mekheimer, A. M. Abdel Hameed, S. A. A.

View Article Online
DOI: 10.1039/C6RA11171H

Mansour and K. U. Sadek, *Chin. Chem. Lett.* 2009, **20**, 812; (r) X. B. Wang, L. He, T. Y. Jian and S. Ye, *Chin. Chem. Lett.* 2012, **23**, 13; (s) A. Teimouri and A. N. Chermahini, *J. Mol. Catal. A: Chem.* 2011, **346**, 39; (t) A. Davoodnia, M. M. Heravi, Z. Safavi-Rad and N. Tavakoli-Hoseini, *Synth. Commun.* 2010, **40**, 2588; (u) A. R. Moosavi-Zare, Zh. Asgari, A. Zare, M. A. Zolfigol and M. Shekouhy, *RSC Adv.* 2014, **4**, 60636; (v) M. R. Mohammadizadeh, A. Hasaninejad and M. Bahramzadeh, *Synth. Commun.* 2009, **39**, 3232; (w) A. Hasaninejad, A. Zare, M. Shekouhy and J. Ameri Rad, *J. Comb. Chem.* 2010, **12**, 844.

15. (a) A. Khalafi-Nezhad, M. Divar, F. Panahi, *RSC Adv.* 2015, **5**, 2223; (b) A. Khalafi-Nezhad, M. Nourisefat, F. Panahi, *Org. Biomol. Chem.* 2015, **13**, 7772; (c) M. Nourisefat, F. Panahi and A. Khalafi-Nezhad, *Org. Biomol. Chem.* 2014, **12**, 9419; (d) M. Shekouhy, A. Masoudi Sarvestani, S. Khajeh and A. Khalafi-Nezhad, *RSC Adv.* 2015, **5**, 63705; (e) M. Shekouhy, A. Moaddeli and A. Khalafi-Nezhad, *Res. Chem. Intermed.* 2016, **42**, 3805; (f) M. Shekouhy, A. Khalafi-Nezhad, *Green Chem.* 2015, **17**, 4815.

16. (a) A. Hasaninejad, A. Zare, M. Shekouhy and J. Ameri-Rad, *Green Chem.* 2011, **13**, 958; (b) M. Shekouhy, *Catal. Sci. Technol.* 2012, **2**, 1010; (c) P. Salehi, M. A. Zolfigol, F. Shirini and M. Baghbanzadeh, *Curr. Org. Chem.* 2006, **10**, 2171.

17. (a) A. Zare, A. Parhami, A. R. Moosavi-Zare, A. Hasaninejad, A. Khalafi-Nezhad and M. H. Beyzavi, *Can. J. Chem.* 2009, **87**,416; (b) C. O. Kappe, *Angew. Chem., Int. Ed.* 2004, **43**, 6250.

18. B. L. Korbad and S. H. Lee, *Bull. Korean Chem. Soc.* 2013, **34**, 1266.